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EXAMINER
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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 26

Application Number: 09/320,156

Filing Date: May 26, 1999

Appellant(s): Rosenblum et al

Benjamin A. Adler

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed January 17, 2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The Brief contains a statement that Appellant does not know of any pending related appeals or interferences that would affect or be affected by the present appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct as of the Advisory Action of Paper No. 22. However, upon review and reconsideration, the rejection of claim 18 is withdrawn. Claim 18 is now objected to for being dependent on a rejected claim.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 15-19 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

No new prior art of record is relied upon by the examiner.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim 15 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bacus et al (USP 5,514,554, effective filing date 9/27/91) in view of Rosenblum et al (Cancer Communications, 1991) and Hudziak et al (Molecular and Cellular Biology, 1989). Claim 15 and 19 are drawn to a composition comprising a conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, and pharmaceutical compositions thereof. Bacus et al teach ricin A conjugated via SPDP chemistry to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, also known as Her-2 receptor. Rosenblum et al teach tumor necrosis factor conjugated via SPDP chemistry to an antibody which binds specifically to epitope A of gp240 antigen found on the surface of melanoma cell lines and fresh tumor samples. Rosenblum et al do not teach the conjugate of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak et al teach an anti-$p185^{HER2}$ /anti-c-erbB-2 monoclonal antibody which increases the sensitivity of $p185^{HER2}$ expressing tumor cells to the cytotoxic effects of TNF.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to conjugate TNF via SPDP chemistry to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein. Hudziak has demonstrated that cells expressing HER-2/c-erbB-2 showed increased resistance to the cytotoxic effects of TNF and that this resistance can be overcome by the co-administration of an anti-proliferative antibody directed against the extracellular portion of the c-erbB-2 protein. Rosenblum discloses improved tumor-targeting of TNF to target cell lines by the use of an antibody which binds specifically to the extracellular portion of the target polypeptide conjugated tumor necrosis factor by SPDP conjugation.

One of ordinary skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Bacus in view of Rosenblum and Hudziak. One of skill in the art would have been motivated to conjugate TNF with an antibody directed against the extracellular epitope of c-erbB-2 protein to attain an anti-proliferative and heightened cytotoxic effect as taught by Hudziak and an improvement in the tumor-targeted delivery of TNF as taught by Rosenblum. Rosenblum teaches that TNF retains activity after SPDP conjugation, therefore the chemical conjugation did not disrupt the domains of TNF essential to its function. Bacus et al teach that the anti-c-erb-B2 antibody conjugated to ricin A by means of SPDP chemistry retains its affinity to the c-erbB-2, thus the SPDP chemical conjugation to ricin A did not disrupt the binding site of the antibody or adversely affect the specific targeting of the SPDP formed conjugate.

Claims 15, 16, 17 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wels et al (USP 5,571,894, effective filing date 7/15/91) in view of Hoogenboom et al (Biochimica et Biophysica Acta, 1991, Vol. 4, pp. 345-354 and Hudziak et al (Molecular and Cellular Biology, 1989). Claims 15, 16, 17 and 19 are drawn to a composition comprising a fusion of tumor necrosis factor to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein, and pharmaceutical compositions thereof, wherein said fusion protein is recombinantly produced. Wels et al teach a recombinant single chain antibody directed toward the extracellular portion of c-erbB-2 fused to a effector useful for therapeutic purposes such as toxins or other drugs (column 3, lines 12-37). Wels et al do not specifically teach TNF as an effector molecule fused to the anti- c-erbB-2 single chain antibody. Hoogenboom et al teach a recombinant antibody-TNF fusion protein. Hudziak et al teach an anti-$p185^{HER2}$ /anti-c-erbB-2 monoclonal antibody which increases the sensitivity of $p185^{HER2}$ expressing tumor cells to the cytotoxic effects of TNF. It would have been *prima facie* obvious to one of ordinary skill in the

art at the time the claimed invention was made to make a recombinant fusion protein of TNF and the single chained anti-c-erbB-2 antibody. One of ordinary skill in the art would have been motivated to conjugate TNF to a single chained antibody directed against the extracellular epitope of c-erbB-2 protein with a reasonable expectation of success by the teachings of Wels in view of Hoogenboom and Hudziak. Hudziak teaches the combined administration of an antibody directed against an extracellular epitope of c-erbB-2 protein and TNF to attain an anti-proliferative and heightened cytotoxic effects. Wells et al teach the advantages of recombinantly expressed single chained antibody directed against an extracellular epitope of c-erbB-2 protein and fusion proteins thereof. Hoogenboom teaches the recombinant expression of general antibodies fused to TNF.

(11) Response to Argument

Appellant argues that given the structural specificity and precision in the process of protein folding that define each proteins activity, one skilled in the art would not be motivated to combine the teachings of the prior art references with any expectation of success in obtaining the particular composition in the present claims while retaining both antibody binding and cytotoxic activity. Appellant sites the encyclopedia of molecular Biology, 1994 which states that "the biological activity of a protein depends on the folding of its amino acid chain(s) into a highly organized, precise three dimensional structure under physiological conditions. The examiner agrees with this statement. Appellant states that Hudziak teaches the administration of an un-conjugated monoclonal anti-erbB2 antibody and tumor necrosis factor for the sensitization of breast cancer cells to tumor necrosis factor. Appellant maintains that from this, one of skill in the art could not determine from the teachings of Wels or Hoogenboom and Hudziak whether a fusion protein between tumor necrosis factor and a single chain anti-erbB2 antibody would retain antibody binding. Appellant states that it was likely that the fusion process would result in the disruption of the specific process of protein folding necessary for the separate proteins to function properly. Appellant cites Freidman et al wherein it was demonstrated that a single chained

antibody fused to an exotoxin was five fold less effective than the native antibody in binding to the target antigen (Friedman et al, page 336, first column first paragraph under the heading "Binding Activity of BR96 sFv-PE40 towards Lewis(y) antigen"). This has been considered but not found persuasive. The comparison between the single chain immunotoxin and the native antibody dose not reflect a loss of binding activity due to the fusion with the endotoxin because the comparison has not taken into account the relative binding affinity of the single chain antibody relative to the full antibody. Further, Friedman teaches that the issue was how a monovalent single chained antibody would differ in binding affinity from a bivalent antibody (Friedman, page 337, second paragraph under the heading of "Discussion"). However, of the instant prior art reference of Wels (US 5,571,894) teaches single chained antibodies which bind to c-ErbB2 (for example column 3, lines 11-37 and column 6, line 54 to column 7, line 31), therefore one of skill in the art would know that the single chained antibodies of Wels were useful in the binding of the c-erbB2 antigen. Regarding the issue of the modification by attachment of the tumor necrosis factor protein. Appellant argues that Chaudhary et al measured the affinity of the fusion protein between a single chain antibody and an exotoxin and found that it exhibited a three-fold decrease in comparison to the un-fused antibody (Chaudhary et al, page 396, second to last paragraph). This has been considered but not found to be persuasive. Freidman et al teach that the fusion between the single chained antibody and the exotoxin resulted in a five fold decrease in binding affinity relative to the un-modified full antibody. Friedman et al also teach that this fusion protein had efficacy in the delivery of the toxin to the target cells despite the decrease in affinity (page 334, column 2, second full paragraph). Chaudhary et al also teach the loss in binding affinity does not preclude the use of the fusion protein in the targeting of a cell population (last paragraph). Thus, one of skill in the art would reasonably conclude that based on the teachings of Freidman et al, or Chaudhary et al that a loss in binding affinity of three-fold or five-fold in comparison with the full unmodified antibody, does not inhibit the use of the fusion proteins as targeting molecules for the delivery of toxic moieties to a population of cells. Furthermore, with regard to claim

encompassing antibodies chemically conjugated to toxins, it is noted that Bacus et al teach ricin A conjugated via SPDP chemistry to an antibody exhibiting binding specificity for an extracellular epitope of c-erbB-2 protein (column 15, lines 29-45) and Rosenblum et al teach tumor necrosis factor conjugated via SPDP chemistry to an antibody which binds specifically to an antigen on the surface of melanoma cell lines and fresh tumor samples (bridging paragraph, pages 21-22). In both cases, the chemical conjugation did not destroy binding affinity of the antibody, or function of the toxin. One of skill in the art would reasonably conclude that an antibody directed against c-erbB2 conjugated to tumor necrosis factor would retain enough binding affinity for the target antigen to specifically bind said target within a population of cells.

Appellants arguments and exhibits have been fully and carefully considered, but are not considered sufficient to rebut the prima facie case of obviousness over the prior art and it is believed that the rejections should be sustained.

Respectfully submitted,

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